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Clinical efficacy of combination therapy of *FuXi-Tiandi-Wuxing Decoction* and anti-viral drugs in the treatment of novel coronavirus pneumonia: A prospective interventional study

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ABSTRACT

Introduction: The National Administration of Traditional Chinese Medicine of the People's Republic of China (NATCM) and the State Administration of Traditional Chinese medicine (TCM) advocated a combination therapy of TCM and anti-viral drugs for novel coronavirus pneumonia (NCP) to improve the efficacy of clinical treatment.
Methods: Forty-six patients diagnosed with NCP were sequentially divided into intent-to-treat population: the experimental group (combination of *FuXi-Tiandi-Wuxing Decoction* and anti-viral drugs; n = 23) and the control group (anti-viral drugs only) (n = 23). The two groups were compared in terms of duration of fever, cough symptom score, fatigue, appetite, dyspnea, out-of-bed activities, chest computer tomography (CT) recovery, virological clearance, average length of hospital stay, and clinical effective rate of drug. After 6 days of observation, patients from the control group were divided into as-treated population: experimental subgroup (n = 14) to obtain clinical benefit and control subgroup (n = 9).
Results: There was a significant improvement in the duration of fever (1.087 ± 0.288 vs 4.304 ± 2.490), cough (0.437 ± 0.589 vs 2.435 ± 0.662; $P < 0.05$), chest CT evaluation (82.6% vs 43.4%; $P < 0.05$), and virological clearance (60.8% vs 8.7%; $P < 0.05$) in patients of the experimental group compared with patients in the control group. Further observation in as-treated population reported that cough (0.742 ± 0.463 vs 1.862 ± 0.347; $P < 0.05$) and fatigue (78.5% vs 33.3%; $P < 0.05$) were significantly relieved after adding *FuXi-Tiandi-Wuxing Decoction* to the existing treatment.
Conclusion: An early treatment with combination therapy of *FuXi-Tiandi-Wuxing Decoction* and anti-viral drugs significantly relieves the clinical symptoms of NCP, shows improvement in chest CT scan, improves virological clearance, shortens average length of hospital stay, and reduces the risk of severe illness. The effect of *FuXi-Tiandi-Wuxing Decoction* in NCP may be clinically important and require further consideration.

1. Introduction

Recently, an outbreak of a new type of coronavirus identified as novel coronavirus pneumonia (NCP) or 2019-nCov or COVID-19 occurred in Wuhan, Hubei Province, China, in December 2019 (Munster et al., 2020; Zhou et al., 2020). Since then, the epidemic has spread rapidly to other cities of China and to many other countries around the world by early February 2020 (Munster et al., 2020; Ge et al., 2020) The outbreak was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on January 30, 2020 ("Statement on the second meeting of the International Health Regulations, 2005 Emergency Committee regarding the outbreak of

Abbreviations: ARDS, acute respiratory distress syndrome; CRS, cytokine release syndrome; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; H1N1, Hemagglutinin Type 1 and Neuraminidase Type 1; ITT, intent-to-treat; NATCM, National Administration of Traditional Chinese Medicine of the People's Republic of China; NCP, novel coronavirus pneumonia; PG, Platycodon grandiflorum; RdRp, RNA-dependent RNA polymerase; RT-PCR, reverse transcriptase polymerase chain reaction; TCM, traditional Chinese medicine; TNF, tumor necrosis factor; WHO, World Health Organization.

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novel coronavirus (2019-nCoV)," n.d.). As of July 16, 2020, WHO has reported 13,378,853 total number of diagnosed cases and with 580,045 deaths worldwide ("Coronavirus Disease (COVID-19) Situation Reports, " n.d.). Approximately 14–16% of patients with NCP have acute respiratory distress, cytokine storm, higher leucocyte numbers, and abnormal respiratory findings while 5% of patients become critically ill (Rothan and Byrareddy, 2020; Shang et al., 2020; Ye et al., 2020). The mortality rate among those patients having critical illness was reported to be over 50% ("Coronavirus Disease (COVID-19) Situation Reports," n.d.). The disease has been included in the class B infectious disease as stipulated in the law of the People's Republic of China on the prevention and control of infectious diseases and is managed as an infectious disease belonging to class A (Pei-Fang, 2020).

The pathogenic mechanism that induces pneumonia seems to be complex and is associated to inflammatory response (Cascella et al., 2020). The viral infection is capable of producing an extreme immune reaction in the host, termed as "cytokine storm" due to interleukin (IL)−6 (Cascella et al., 2020). IL-6 is produced mostly by activated leukocytes and promotes the differentiation of B lymphocytes and inhibits the growth of other cells (Cascella et al., 2020). It is also implicated in the pathogenesis of the cytokine release syndrome (CRS) that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction (Cascella et al., 2020). The main clinical manifestations of the patients include fever, fatigue, and dry cough (Pei-Fang, 2020). A few patients have nasal obstruction, runny nose, sore throat, and diarrhea. Most of the patients often have dyspnea and hypoxemia one week after the onset of the disease (Pei-Fang, 2020). Furthermore, the condition in these patients can rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, and coagulation dysfunction that are difficult to correct and multiple organ failure, which may endanger life (Pei-Fang, 2020). The elderly and those with chronic underlying disease such as diabetes, hypertension, cardiovascular, and other diseases may be critically ill after developing infection, while the children and neonatal patients may show symptoms such as nausea or vomiting, lethargy, or shortness of breath (Pei-Fang, 2020). Several critically ill patients may only present with moderate to low fever, or even no fever at all (National Administration of TCM, 2020; Pei-Fang, 2020).

There is no effective antiviral drug for NCP infection at present and the current clinical treatment relies mainly on symptomatic treatment (National Administration of TCM, 2020; Pei-Fang, 2020). The efficacy of new therapeutics remains inconclusive. In this context, adopting unconventional approaches is urgently needed. Currently, National Institute of Health guidelines has proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate symptoms of NCP. Other treatment under investigation include anti-viral drugs mainly remdesivir, lopinavir/ritonavir, umifenovir and favipiravir; chloroquine and hydroxychloroquine; immunomodulators, such as tocilizumab and interferon-β-1a; plasma therapy ("Clinical management of COVID-19," n.d.; "COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health.," n.d.). Ju et al. believe that sofosbuvir/velpatasvir is a potential drug to inhibit NCP virus, by inhibiting RNA-dependent RNA polymerase (RdRp) (Ju et al., 2020). Recently, a study showed that remdesivir may be a specific targeted drug with a great potential for inhibiting NCP (Wang et al., 2020). Various in vitro and animal studies also proved the efficacy of various anti-viral drugs to have good inhibitory effects on SARS-CoV and MERS-CoV (Sheahan et al., 2020, 2017).

In 2003, traditional Chinese medicine (TCM) were used in combating SARS-infected atypical pneumonia in China and provided a valuable experience (Hsu et al., 2006; Lau et al., 2005; Poon et al., 2006; Zhong and Zeng, 2003). Lau et al. reported that using TCM herbal extract namely *Sang Ju Yin* plus *Yu Ping Feng San* could modulate T cells to enhance host defense capacity and thus cure patients infected by SARS (Lau et al., 2005). Another study reported that TCM as a supplementation resulted in marked improvement of symptoms and shortened the disease course (Hsu et al., 2006). Therefore, after the recent outbreak, the National Administration of Traditional Chinese Medicine of the People's Republic of China (NATCM) and the State Administration of TCM jointly issued a document advocating the combination therapy of TCM and anti-viral drugs, to help improve the efficacy of clinical treatment, shorten the course of the disease, and reduce the incidence of severe/critical cases (National Administration of TCM, 2020; Pei-Fang, 2020) According to the NATCM, the total effective rate of certain TCM prescription for NCP is over 90% ("National Administration of Traditional Chinese Medicine. Progress has been made in the screening of effective prescriptions for traditional Chinese medicine.," n.d.). Zhang Boli and their colleagues found that the integration of TCM and anti-viral drugs is beneficial in alleviating clinical symptoms, improving CT imaging of lungs, and virological clearance into positive in severe cases (Xia et al., 2020). Miao Qing et al. also believe that TCM injection in the early stage of lung infection is conducive to the rapid and comprehensive recovery of patients (Qing et al., 2020).

A recent meta-analysis also underlined the effectiveness of TCM in improving clinical symptoms of NCP (Zeng et al., 2020). Despite these noteworthy findings, randomized clinical trials with TCM and anti-viral drug combination is warranted to authenticate the effectiveness of this combination therapy. Use of TCM as a monotherapy or adjuvant therapy may offer unique insights to inform scientific studies and empirical research in order to solve the global crisis with grave health, economic and social impacts. At this juncture, in view of the potential benefits of TCM for treating NCP, the authors team conducted an interventional study by collecting real-world clinical data of patients with NCP for research, evaluated the efficacy of combination of TCM with anti-viral drugs with constant treatment plan adjustment and summarized the experience, so as to provide a basis for promoting the greater role of TCM in the fight against the epidemic.

2. Material and methods

2.1. Study design

This study was a prospective, interventional study where 46 patients were enrolled with confirmed diagnosis of NCP in Xiangzhou District People's Hospital of Xiangyang, Hubei Province, China, from February 1, 2020 to March 1, 2020. The experimental group (n = 23) were given a combination of a novel TCM labeled "*FuXi-Tiandi-Wuxing Decoction*" along with anti-viral drugs, whereas the control group (n = 23) were given anti-viral drugs alone. Patients belonging to the control group were further divided after 6 days into the experimental subgroup (n = 14) receiving combination therapy of *FuXi-Tiandi-Wuxing Decoction* and anti-viral drugs, whereas the control subgroup (n = 9) continued to receive anti-viral drugs. Further, the remaining 9 patients already on anti-viral drugs were treated with *FuXi-Tiandi-Wuxing Decoction* when there was no improvement in their symptoms. The study timeline and treatment plan for the two groups are provided in Fig. 1.

This study was approved by the ethics committees of Xiangzhou District People's Hospital of Xiangyang, Hubei Province, and was conducted in accordance to the 1964 Helsinki Declaration. All the patients gave written consent for participating in the study.

2.2. Diagnostic criteria for eligible patients

The patients were included in the study based on the Diagnosis and Treatment Program of 2019 NCP program formulated by National Health Commission of China (National Administration of TCM, 2020; National Administration of TCM, 2020; National Administration of TCM, 2020; Pei-Fang, 2020). The choice of treatment was determined by the clinical experience of physicians and by the patient preference. The study was mainly to assess the curative effect of the TCM either alone or with anti-viral drugs.

Briefly, the inclusion criteria were as follows: (a) patients with any of

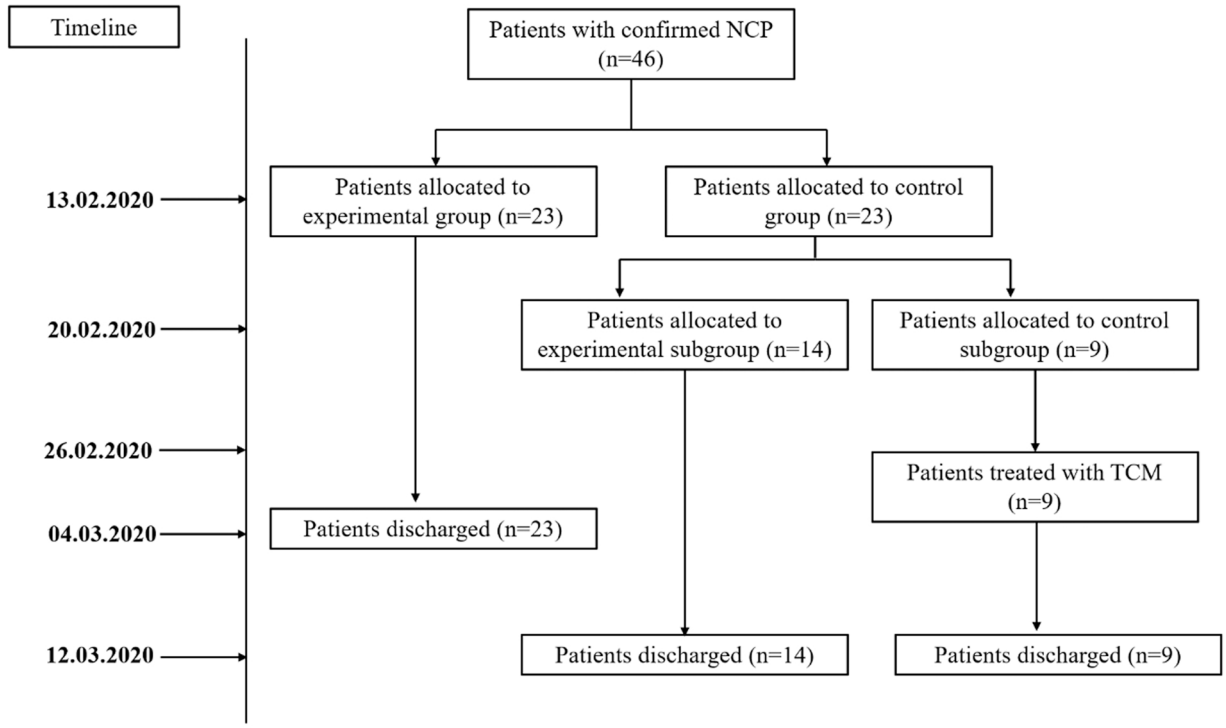

Fig. 1. Study timeline and treatment plan.

the epidemiological history (travel and/or residence history in Wuhan or exposure history to patients with fever and respiratory symptoms from Wuhan within 14 days before the onset of illness) (b) two or all three clinical manifestations (fever, imaging characteristics of pneumonia, and/or normal or decreased white blood cell count or decreased lymphocyte count) (c) laboratory diagnosis as determined by real-time fluorescent polymerase chain reaction (RT-PCR) or next-generation sequencing (NGS) methods or serological findings by immunoglobulin M (IgM) and IgG serum concentration via ELISA. According to the clinical manifestations, confirmed patients were divided into mild, moderate, and severe cases. Other criteria were patients with respiratory distress ($\geq$30 breaths/min); oxygen saturation $\leq$ 93% at rest; arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) $\leq$ 300 mmHg, lesion progression of $>$ 50% through chest imaging within 24–48 h (National Administration of TCM, 2020; National Administration of TCM, 2020; National Administration of TCM, 2020; Pei-Fang, 2020). Due to the growing pandemic, most of the patients were already confirmed with COVID-19 and hence the authors could include only a small sample size of diagnosed patients in the study.

2.3. Dosage and treatment regimen

2.3.1. Western medicine treatment

Patients in the control group (n = 23) received anti-viral drugs [alpha-interferon (5 million U or equivalent dose twice daily), arbidol (200 mg thrice a day, no longer than 10 days), lopinavir/ritonavir (200 mg/50 mg per pill, two pills each time, twice daily, no longer than 10 days), ribavirin (to be used jointly with interferon or lopinavir/ritonavir, 500 mg, twice or three times of intravenous injection daily, no longer than 10 days)] according to the New Coronavirus Pneumonia Diagnosis and Treatment Program (National Administration of TCM, 2020; National Administration of TCM, 2020; National Administration of TCM, 2020; Pei-Fang, 2020). In addition, antimicrobial drugs (penicillin, cephalosporins, levofloxacin) were given to patients with bacterial infections.

2.3.2. TCM preparation and treatment

According to the TCM theory and the recommendations of the diagnosis and treatment guide for COVID-19 issued in China, the research team formulated a *FuXi-Tiandi-Wuxing Decoction* which consisted of 10 different herbs. All these herbs are commonly available and prepared according to specifications mentioned in Chinese Pharmacopeia. Patients in the experimental group (n = 23) were treated with a combination of the above anti-viral drugs along with "*FuXi-Tiandi-Wuxing Decoction*," the main ingredients were *Lonicera japonica* Thunb, *Taraxacum mongolicum* Hand.-Mazz, *Aucklandia lappa* Decne, *Lithospermum erythrorhizon* Sieb. et Zucc, *Agastache rugosa* (Fisch. et Mey.) O. Ktze, *Pseudostellaria heterophylla(Miq.), Glycyrrhiza uralensis* Fisch, *Astragalus membranaceus* (Fisch.) Bunge, *Dendranthema morifolium*, and *Platycodon grandiflorus* (Jacq.) A. DC.

. This medicine was given for 3 days in a dose of 1.5 bottles/day, after or with a meal after warming the bottle with warm water. The *FuXi-Tiandi-Wuxing Decoction* was provided by Beijing 709 Medical Research Institute, supplied to the participating sites, and dispensed by the designated research nurses after the patients were allotted to the respective groups.

2.4. Outcomes

The primary outcomes assessed were duration of fever, cough symptom score, chest CT evaluation, and virological clearance, whereas the secondary outcomes included other clinical symptoms such as asthenia, shortness of breath, anorexia, doing out-of-bed activities, and length of hospital stay. These outcomes were monitored during the stays in the hospital. The clinical cure rate and clinical effectiveness of the drug was also evaluated. The outcomes criteria were defined according to the NHC-NATCM-China guidelines (National Administration of TCM, 2020; National Administration of TCM, 2020; National Administration

of TCM, 2020; Pei-Fang, 2020) and the Chinese Guidelines for Diagnosis and Management of Cough (Chung, 2006; Irwin, 2006; Lai K, 2008) as presented in Tables 1 and 2 by a blinded assessor.

2.5. Statistical analysis

Data for continuous variables were expressed by mean ± standard deviation (x ± S.D). Continuous variables were compared using independent sample t-test; categorical data were expressed as frequencies. Comparisons of the primary and secondary outcomes at the end of treatment between two groups were performed using Pearson's $\chi 2$ test. $P < 0.05$ was used as the criterion for determining statistical significance. The analysis was based on the intent-to-treat (ITT) principle considering the clinical benefit observed after 6 days, the patients from control group were subdivided (Fig. 1) into experimental and control group and compared for outcomes ('as treated' results).

3. Results

3.1. Baseline and clinicopathological characteristics of patients

Among the 46 patients included for the study, the mean age was 42.48 ± 11.06 years in the experimental group and 47.30 ± 17.79 years in the control group. The other baseline characteristics were comparable between the two treatment groups with no statistically significant differences in gender, basic diseases, and clinical manifestation of symptoms at the initial stage of treatment. Table 3 represents the baseline characteristics between the two treatment groups.

3.2. ITT population

3.2.1. Primary outcomes

The duration of fever was significantly improved in the experimental group compared with the control group (mean ± SD: 1.087 ± 0.288 days vs 4.304 ± 2.490 days; $P < 0.05$) (Table 4). Similar results were obtained when the symptoms of cough were assessed (0.437 ± 0.589 in the experimental group vs 2.435 ± 0.662 in the control group; $P < 0.05$) (Table 4). Results of chest CT scan revealed a significant improvement in the experimental group compared with the control group [(n)%:19 (82.6%) vs 10 (43.4%); $P < 0.05$], which suggested that the healing of exuded lesions and absorption rate with the combination therapy was rapid, whereas it was slow and non-obvious in the control group (Fig. 2 and Table 4). Virological clearance was better and statistically significant in the experimental group than the control group [n (%): 14(60.8%) vs 2(8.7%); $P < 0.05$] (Table 4).

3.2.2. Secondary outcomes

There was a significant improvement in fatigue [22 (95.6%) vs 4 (17.4%], appetite [22 (95.6%) vs 2 (8.7%)] in the experimental group compared with the control group at the end of treatment period ($P < 0.05$). However, there was no significant improvement between the two groups in terms of doing out-of-bed activities [22 (95.6%) vs 19 (82.6%)] and dyspnea [20 (86.9% vs 7 (30.4%)]. Further, the average length of hospital stay was 16.57 ± 2.79 days in patients in the experimental group with a clinical cure rate of 60.8%. In terms of clinical effective rate of treatment, patients in the experimental group showed higher effective treatment than the control group (86.9% vs 52.1%). There were no adverse events observed between the two treatment groups (Table 5).

3.3. As treated population

3.3.1. Primary outcomes

During the course of treatment, after observation for 6 days, it was observed that the combination therapy of *FuXi-Tiandi-Wuxing Decoction* and anti-viral drugs showed better and significant clinical effects in

Table 1
Outcomes measured defined by the criteria.

Outcomes	Predefined criteria
Duration of fever	The time from initiating the medicine to the time when body temperature drops to normal is considered.(Zheng Xiaoyu, 2002)
Cough symptom score scale	Cough symptoms and quantitative scores were evaluated according to the Chinese Guidelines for Diagnosis and Management of Cough (Chung, 2006; Irwin, 2006; Lai K, 2008) Further categories are presented in Table 2.
Symptoms such as asthenia, shortness of breath, anorexia and doing out-of-bed activities	Recovery of the symptoms were analyzed using counting method to calculate the incidence of symptom improvement.
Chest CT evaluation	Four stages of lung involvement were defined on CT scans: early-stage, progressive stage, peak stage, absorption stage. Early stage (stage I): lesions were distributed subpleurally in the lower lobes unilaterally or bilaterally with multiple ground-glass opacities (GGO), with visible lung markings in a grid shape, accompanied by vascular thickening. Progressive stage (stage II): The area of infection rapidly increases and enlarges, and advances from the periphery to the center along the bronchial and vascular margins. The density in the lesion increases, extended to a bilateral multilobe distribution with diffuse GGO, crazy-paving pattern, and consolidation. Peak stage (stage III): manifested as a large area of lung tissue increases in density and dense consolidation becomes more prevalent. Residual parenchymal bands along with diffuse GGO, crazy-paving pattern and consolidation are visible. Absorption phase (stage IV): The lesions were controlled and diffuse GGO was completely absorbed. In addition, pulmonary lesions may lead to changes in fibrosis at this stage.
Virological clearance	Nucleic acid can be detected in nasopharyngeal swab, sputum, lower respiratory tract secretions, blood, feces and other respiratory samples using RT-PCR and/or NGS methods. In addition, NCP virus specific IgM must become detectable around 3–5 days after onset; IgG reaches a titration of at least 4-fold increase during convalescence compared with the acute phase (National Administration of TCM, 2020; National Administration of TCM, 2020; National Administration of TCM, 2020; Pei-Fang, 2020)
Discharge criteria	Body temperature is back to normal for > 3 days, respiratory symptoms improved significantly, pulmonary imaging showed significant absorption of inflammation, two consecutive negative detection of new coronavirus nucleic acid in respiratory tract (sampling time interval of at least 24 h) (National Administration of TCM, 2020; National Administration of TCM, 2020; National Administration of TCM, 2020; Pei-Fang, 2020).
Length of hospital stay	Refers to the time from admission to discharge of patient to hospital. The average length of hospital stay for each group was calculated by statistical software and compared between the two treatment groups.

Table 2
Cough symptom score.

Score	Daytime cough symptom score	Nighttime cough symptom score
0	No cough	No cough
1	Occasional transient cough	Cough briefly or occasionally at night while sleeping
2	Frequent coughing, affecting daily life	Sleep at night due to mild cough
3	Frequent coughing, seriously affecting daily life	Bad night sleep due to cough

Table 3
Baseline characteristics between the two treatment groups.

ITT population	Experimental group (n = 23)	Control group (n = 23)	χ/t^2	P-Value
Gender (n, %)				
Male	12 (52.2)	12 (52.2)	0	1
Female	11 (47.8)	11 (47.8)		
Age (mean ± SD)	42.48 ± 11.06	47.30 ± 17.79	1.11	0.27
Chronic underlying diseases (n, %)				
Diabetes	5 (21.7)	4 (17.4)	0.1381	0.770
Cardiovascular disorder	2 (8.7)	3 (13.0)	0.2244	0.636
Chronic gastritis	2 (8.7)	3 (13.0)	0.2244	0.636
Hypertension	4 (17.4)	3 (13.0)	0.1685	0.681
Clinical symptoms (n, %)				
Fever	23 (100)	22 (95.6)	1.0222	0.312
Cough	19 (82.6)	21 (91.3)	0.7667	0.381
Weakness	15 (65.2)	10 (43.5)	2.1905	0.139
Dyspnea	12 (52.2)	16 (69.6)	1.4603	0.227
Limited activity	10 (43.5)	8 (34.8)	0.3651	0.546
Anorexia	18 (78.3)	21 (91.3)	0.3406	0.559

Table 4
Primary treatment outcomes between the two treatment groups at the end of treatment period (ITT population).

IIT population	Experimental group (n = 23)	Control group (n = 23)	χ/t^2	P
Duration of fever (days)	1.087 ± 0.288	4.304 ± 2.490	t = 6.15	< 0.05
Cough score (mean ± SD)	0.437 ± 0.589	2.435 ± 0.662	t = 10.82	< 0.05
Chest CT scan (n, %)	19 (82.6)	10 (43.4)	$\chi2 = 7.56$	< 0.05
Virological clearance (%)	14 (60.8)	2 (8.7)	$\chi2 = 15.77$	<0.05
Dyspnea improvement (n%)	20 (86.9)	7 (30.4)	$\chi2 = 15.154$	< 0.05
Out-of-bed activity (n, %)	22 (95.6)	19 (82.6)	$\chi2 = 2.019$	< 0.05

patients belonging to the experimental group than the control group. Thus, in order to ensure safety of the patients in the control group as per patient preference and physician recommendation, patients were subdivided further to receive combination of *FuXi-Tiandi-Wuxing Decoction* and anti-viral drugs in the experimental group (n = 14). The remaining nine patients continued to receive anti-viral drugs.

There was a statistically significant improvement in symptoms of cough score after the patients in the experimental group started treatment with *FuXi-Tiandi-Wuxing Decoction* in addition to anti-viral drugs (0.742 ± 0.463 vs 1.862 ± 0.347; P < 0.05). There was no statistically significant difference in the chest CT scan results between the two treatment groups (P = 0.07). Considering that the number of patients in the experimental group were taken from the original control group, the sample size was too small and hence a statistically significant difference could not be achieved after addition of *FuXi-Tiandi-Wuxing Decoction*. However, chest CT scan results were significantly higher in the experimental group (71.4%) than the control group (33.3%). At the end of treatment period, two patients reported to have virological clearance in the experimental group after addition of *FuXi-Tiandi-Wuxing Decoction*. Results are presented in Table 6.

3.3.2. Secondary outcomes

There was a significant improvement in fatigue after addition of *FuXi-Tiandi-Wuxing Decoction* to anti-viral drugs in the experimental group compared with the control group [11 (78.5%) vs 3 (3.3%); P < 0.05]. However, there was no significant differences between the treatment groups compared for improvement in appetite, dyspnea, and out-of-bed activities (P > 0.05). Results are presented in Table 7. At the end of the study period, the average length of hospital stay for the patients in the experimental group (ITT population) (n = 23) was 19.27 ± 6.57 days. The average length of hospital stay was similar in both treatment groups (22.57 ± 5.3 days vs 24.0 ± 7.09 days). The results are as presented in Table 8.

4. Discussion

This study was carried out to evaluate the efficacy of combination therapy of *FuXi-Tiandi-Wuxing Decoction* with anti-viral drugs versus anti-viral drugs alone. In the hospital, the first batch of combination therapy of *FuXi-Tiandi-Wuxing Decoction* and anti-viral drugs were initiated in diagnosed patients with NCP. The main pharmacological effects of this traditional medicine were proposed to clear away heat from the body and detoxification, nourish liver, and improve immune system, strengthen spleen and kidney thereby increasing Yang Qi and eliminating virus, strengthen spleen, and restore lung function. Clinical findings at the end of the study revealed meaningful effect with *FuXi-Tiandi-Wuxing Decoction* with the ability to relieve the main clinical symptoms along with decreased progression of lesions in pulmonary imaging and improve virological clearance. Due to epidemic nature of the disease, the control group was divided into various subgroups till all the patients were cured of the disease. Further, the average length of hospital stay of patients with NCP in the experimental group was shorter than in the control group suggesting that the Chinese medicine used can effectively shorten the pathological evolution of NCP.

These results are consistent with the previously published studies evaluating the efficacy of combination of TCM and anti-viral drugs (Ye and Group, 2020; Zhang et al., 2020). Zhang et al. observed that TCM when combined with Western medicine can shorten the duration of fever and accelerate the absorption of lung lesions in patients with NCP (Zhang et al., 2020). Another prospective randomized study revealed that the disease severity is decreased in NCP patients with TCM than in the standard care group (Ye and Group, 2020). Further, Liu et al. systematically reviewed eight randomized controlled trials and concluded that the combination of TCM with conventional medicine showed beneficial effects such as decrease in mortality and relief of symptoms, together with control of fungal infections in patients with SARS (Liu et al., 2004).

In the theory of TCM, herbal preparations have a potential role in the prevention, treatment, and rehabilitation of respiratory infections, such as NCP through activation of Qi. The mechanisms of action through which Qi functions in the body include stress reduction, emotion regulation, strengthening of respiratory muscles, reduction of inflammation, and enhanced immune function (Feng et al., 2020). Preclinical studies have found that TCM could decrease lung cell apoptosis and reduce the serum content of TNF-alpha in acute lung injury from H1N1 infection (Zhong et al., 2016). *FuXi-Tiandi-Wuxing Decoction* consists mainly of honeysuckle (*Lonicera japonica* Thunb), dandelion (*Taraxacum mongolicum*), platycodon grandiflorum,*Lithospermum erythrorhizon*, chrysanthemum (*Dendranthema morifolium*), liquorice (*Glycyrrhiza uralensis*), *Aucklandia lappa, Agastache rugosa, Pseudostellaria heterophylla, Astragalus membranaceus*. Dandelion has been reported to eliminate heat and

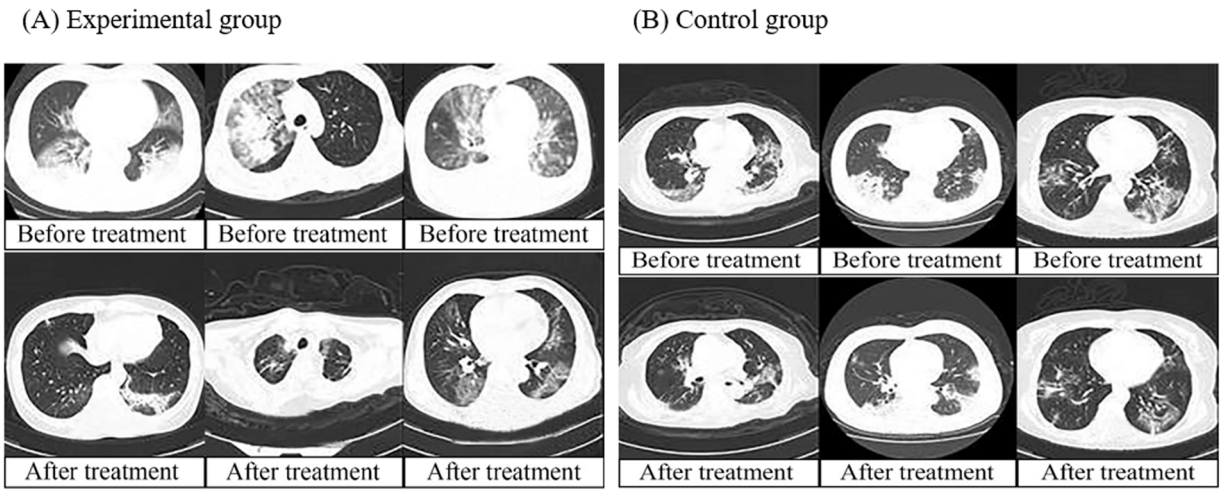

Fig. 2. Chest CT evaluation of patients in (A) the experimental group and (B) the control group before and after 6 days of treatment in the two groups. Patients in both the arms showed single or multiple ground glass density shadows distributed under the pleura, accompanied with bronchial inflation and partial consolidation. After treatment, the lung consolidation significantly improved in TCM group.

Table 5
Secondary treatment outcomes between the two treatment groups at the end of treatment period (ITT population).

IIT population	Experimental group (n = 23)	Control group (n = 23)	χ/t^2	P
Fatigue improvement (n, %)	22 (95.6)	4 (17.4)	$\chi2 = 28.660$	< 0.05
Appetite recovery (n, %)	22 (95.6)	2 (8.7)	$\chi2 = 34.848$	< 0.05
Dyspnea improvement (n, %)	20 (86.9)	7 (30.4)	$\chi2 = 15.154$	
Out-of-bed activities (n, %)	22 (95.6)	19 (82.6)	$\chi2 = 2.019$	
Number of discharged patients (n, %)	14 (60.8)	0	$\chi2 = 22.25$	<0.05
Average length of hospital stay (days, mean ± SD)	16.57 ± 2.79	27.28 ± 6.22	T = 7.535	< 0.0001
Clinical cure rate (%)	60.8	-*	-	-
Clinical effective rate (%)	86.9	52.1	-	-
Adverse events (n)	0	0	-	-

* None of the patients experience clinical cure.

Table 6
Primary treatment outcomes between the two treatment groups at the end of treatment period (as-treated population).

As-treated population	Experimental group (n = 14)	Control group (n = 9)	χ/t^2	P
Cough score (mean ± SD)	0.742 ± 0.463	1.862 ± 0.347	t = 7.482	< 0.05
Chest CT scan (n, %)	10 (71.4)	3 (33.3)	$\chi^2 = 3.23$	0.07
Virological clearance (n, %)	2 (14.28)	0 (0)	$\chi^2 = 1.41$	0.23

Table 7
Secondary treatment outcomes between the two treatment groups at the end of treatment period (As-treated population).

As-treated population	Experimental group (n = 14)	Control group (n = 9)	χ/t^2	P
Fatigue improvement (n, %)	11 (78.5)	3 (33.3)	χ^2 =4.71	<0.05
Appetite recovery (n, %)	12 (85.7)	7 (77.8)	χ^2 = 0.01	> 0.05
Dyspnea improvement (n, %)	13 (92.8)	5 (55.5)	χ^2 = 2.62	> 0.05
Out of bed activity (n, %)	14 (100%)	9 (100%)	χ^2 = 2.62	> 0.05

Table 8
Average length of hospital stay and number of patients with severe illness between two treatment groups (As-treated population).

As-treated population	Experimental group (n = 23)	Control group (n = 9)	
		Experimental group (n = 14)	Control group (n = 9)
Average length of hospital stay (days, mean ± SD)	19.27 ± 6.57	24.0 ± 7.09	22.57 ± 5.35
Patients with severe illness (n, %)	0	2 (14.28%)	3 (33.3%)

toxins, as well as to reduce swelling, choleresis, diuresis, and inflammation and has shown efficacy in the treatment of influenza (He et al., 2011; Sweeney et al., 2005). *Platycodon grandiflorum* (PG) exhibits multiple biological effects, including anti-tumor, anti-inflammation, and anti-obesity properties (Li et al., 2015). Preclinical studies have confirmed its role as an immune enhancer (Noh et al., 2019). Liquorice has the ability to nourish qi, alleviate pain, tonify spleen and stomach, eliminate phlegm, and relieve coughing (Zeng et al., 1988). Various studies have established the efficacy of liquorice in ameliorating respiratory symptoms (Ghorashi et al., 2017; Hocaoglu et al., 2011). Chrysanthemum upregulates of antioxidant enzymes and downregulates of NF-κB and some proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6 (Wu et al., 2014). *Aucklandia lappa,*(gastrointestinal inflammatory diseases (He et al., 2022)), *Agastache rugosa (antioxidant*(Yeo et al.,

2021)) *Pseudostellaria heterophylla* (immune function (Kan et al., 2022)), and *Astragalus membranaceus* (Antifatigue and Anti-Inflammatory (Huang et al., 2022)) are known to have broad-spectrum pharmacological activities. Therefore, according to the theory of TCM and modern Western medical research, treatment with *FuXi-Tiandi-Wuxing Decoction* might have exhibited beneficial effects on NCP.

As suitable treatment options for NCP are limited, this clinical study is mainly for clinicians to provide an insight and possible therapeutic strategy fighting against the epidemic disease. There are some confounding factors in our study including the small sample size, lack of randomization, and a single center trial. However, the assessors were blinded till data analysis and unblinding was carried out later. Also, the mechanism of the action of TCM needs further study and clarification. Although this study reported less adverse events with combination of TCM and anti-viral drugs, the possibility of herb-drug interaction cannot be ruled out. By interacting with conventional medication, herbal medicine may precipitate manifestations of toxicity or in the other extreme, therapeutic failure. The major underlying mechanism of herb-drug interaction is either the induction or inhibition of intestinal and hepatic metabolic enzymes. Additionally, similar effect on drug transporters and efflux proteins particularly the p-glycoproteins in the intestines is responsible in most other cases (Fasinu et al., 2012; Kahraman et al., 2020). As with other studies with smaller sample size, a natural manifestation of disease development may influence clinical outcome despite close monitoring. Despite these limitations, this study provides an opportunity to better understand the role of TCM against NCP. The combination of TCM and anti-viral drugs thus plays an important role in the fight against NCP in China and is expected to play a greater role in the global fight against the epidemic.

5. Conclusion

In conclusion, the authors preliminary observations suggest that early treatment with "*Fuxi-Tiandi Wuxing Decoction*" in combination with anti-viral drugs in patients with NCP can significantly alleviate clinical symptoms of the disease, reduced the progression of lesions, improve the virological clearance and shortening the average length of hospital stay.

Ethical Statement

This study was approved by the ethics committees of Xiangzhou District People's Hospital of Xiangyang, Hubei Province, and was conducted in accordance to the 1964 Helsinki Declaration. All the patients gave written consent for participating in the study.

CRediT authorship contribution statement

Chen Feng: Conceptualization, Methodology, Writing – original draft preparation. **Yao Wenlin**: Investigation, Data curation, Formal analysis, Visualization, Writing – original draft. **Kou Qiangyong**: Visualization, Investigation, Data curation. **Lanting Li**: Validation, Resources, Supervision. **Qi Jingjing**: Data curation, Writing – review & editing.

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Conflict of interest

The authors do not have any conflicts of interest.

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